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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,055	BURCH ET AL.	
	Examiner	Art Unit	
	Padmashri Ponnaluri	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 47-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/21/05 has been entered.

Status of the Claims

2. New claims 51-56 have been added, claim 39 has been canceled by the amendment filed on 7/21/05.

3. Claims 38, and 47-56 are currently pending and under consideration.

Priority

4. This application is a continuation of 09/154,354, which claims benefit of 60/059,195.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 38, 47-48, 50-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,569,937 (Baker et al) and Penning et al (J. Med. Chem. 1997, 40, 1347-1365).

The instant claim briefly recites a method of treating pain in humans comprising orally administering a human patient oral dosage form comprising analgesic compounds consisting essentially of (i) celecoxib and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of : a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and b. ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof, in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47:See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 56).

The Baker reference teaches oral administration, which can be co administered in a single dosage form (e.g. see col. 3-8) or sequentially administered (e.g. see i.e. col. 8-9; mice are dosed sequentially). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4), which include "sustained release carriers". The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is unexpectedly enhanced or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the

individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or Naiads such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32. Accordingly, Baker would teach the use of therapeutic and sub therapeutic amounts of oxycodone and/or ibuprofen in view of the additive or synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

Baker et al further teach in view of the test results of analgesic activities of oxycodone and ibuprofen, it is possible to predict the range of maximum potentiating dosages for man, and utilizing the data from the present invention and the equivalent ratios in man, it is predicted that oxycodone amounts and the ratio of the oxycodone and ibuprofen for the oral dosage in man (i.e., see columns 12-13).

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of celecoxib for ibuprofen into the Baker compositions.

Penning et al. teach both *in vitro* and *in vivo* (up to phase 2 clinical trials) that the selective COX2 inhibitor celecoxib (SC-58635): a. had potent anti-inflammatory activity equivalent to standard NSAID's without the gastric toxicity side-effect of the standard NSAID's (e.g. celecoxib had no acute GI toxicity in rats at doses of up to 200 mg/kg and no chronic GI toxicity at doses up to 600 mg/kg) (see page 1353) (refers to the instant claims 51-55); b. has good bioavailability, is well distributed, and has an excellent safety profile; c. is at least as potent

against pain as aspirin in a phase 1 human clinical dental pain study. See Penning abstract (see last paragraph bridging the page 1353 and 1354).

Accordingly, one of ordinary skill in the art would have been motivated to substitute celecoxib for ibuprofen in the Baker reference compositions in light of the Penning reference teaching that celecoxib is analgesically potent with less side effects (e.g. as compared to NSAIDS e.g. ibuprofen) in both *in vitro* and *in vivo* models, including humans.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting celecoxib for ibuprofen in Bakers composition in light of the benefits of celecoxib (potent analgesia/decreased side effect as compared to NSAID e.g. ibuprofen) as taught by the Penning reference.

8. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. '937 and Penning et al. as applied to claims 38, 46-48 and 50-56 above, and further in view of Oshlack et al. US Pat. No. 5,472,712 (12/95) or Oshlack et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier).

The substance of the above obviousness rejection is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference fails to explicitly teach "a sustained release carrier which provides a sustained release of the oxycodone and/or ... salt thereof".

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone which utilize sustained release carriers employing beads which are coated with the opioid drug or which include substrate layers which include the drugs is known in the art to effectuate delayed release of extended duration. E.g. see Oshlack et al. and Oshlack patent references.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize sustained release carriers for oxycodone including beads/layers as taught by the Oshlack and Oshlack et al. patents for use in the Baker compositions since Baker specifically teaches using "sustained release formulations" and further in view of the advantages of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration.

Response to Arguments

9. Applicant's arguments filed on 7/21/05, regarding the rejection of claims over Baker and Penning et al have been fully considered but they are not persuasive.

Applicants traverse the rejection. Applicants argue that one skilled in the art would not be motivated to substitute the ibuprofen of the formulations of Baker et al with Celecoxib in view of Penning et al.

Applicants arguments regarding this rejection has been addressed in the Advisory Office action mailed on 6/14/05, which is hereby incorporated by reference in its entirety.

Applicants traverse the rejection and further argue that the Background of Baker reference in combination with the secondary references do not teach or suggest the presently claimed invention.

Applicants arguments regarding the Baker reference has been fully considered and are not persuasive, and is considered as response based on a single reference, whereas the rejection is based on combined teachings of more than one reference. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further applicants argue that the Baker reference teaches that ibuprofen provides a synergistic effect in combination with narcotic analgesics, and teaches away from substituting the ibuprofen with celecoxib as suggested by the examiner.

Applicants arguments have been considered and are not persuasive, because Baker et al teach in general the well known combinations of non-steroidal anti-inflammatory drug (NSAID) and narcotic analgesic (in the Background of Invention), and further teach the pharmaceutical compositions of narcotic analgesics and ibuprofen. Ibuprofen is well known member of NSAID, and Penning et al teach that the Celecoxib has more or equivalent potency to that of standard NSAIDs and has no acute GI toxicity upto 200 mg. Thus, it would have been obvious to one skilled in the art at the time the invention was made to use Celecoxib taught by Penning et al and

(another well known NSAID for ibuprofen) in place of ibuprofen in the pharmaceutical compositions taught by Baker et al. Baker et al teachings motivated one skilled in the art to use the combination of ibuprofen (NSAID) with oxycodone. Thus, in the Baker et al there is some teaching, suggestion, or motivation to combine NSAID with oxycodone and in the knowledge generally available to one of ordinary skill in the art (i.e., **background of Baker reference**). See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). And further the Background Section of Baker reference does not teach that NSAIDs known in the art other than Ibuprofen would have synergistic effect, such that the disclosure is considered as teaching away reference.

Applicant's interpretation of the Baker patent reference fails to consider the Baker patent teaching as a whole to one of ordinary skill in the art:

> "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998).

Accordingly, the Baker teaching includes Baker's entire specification and claims, inclusive of Baker's summary of the state of the prior art as illustrated in the "The Background of the Invention" (col. 1-2). In this respect, Baker '936 (col. 1-2) cites numerous prior art references starting with Sunshine et al. for the premise of making analgesic compositions by combining NSAID"s with narcotic analgesic (distinguished by merely additive analgesic effect)

as well as other NSAID's (e.g. acetaminophen etc) with various narcotic analgesics, most notably oxycodone. Baker's invention (e.g. following the summary) is distinguished from the prior art by selecting compositions comprising ibuprofen as the NSAID in combination with narcotic analgesics (including oxycodone) in synergistically effective amounts while reducing the amounts of the narcotic analgesic thus addressing the problem of addiction (pointed to at the end of the "Background of the Invention").

In light of the "Background of the Invention" and lack of any evidence that substitution with a different NSAID would render pain treatment inoperative applicant's teaching away argument is not understood. At most, the selection of a different NSAID may lead to less than synergistic pain relief (e.g. additive) and as such may be "less preferred". In this regard, however, it is noted that:

> Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See also MPEP 2121.04.

Accordingly, for the reasons recited above and for the reasons already of record, the obviousness rejections of record are hereby maintained.

10. Applicant's arguments filed on 7/21/05, regarding the obviousness rejection of claim 49 over Baker et al, Penning et al and Oshlack et al, have been fully considered but they are not persuasive.

Applicants argue that Oshlack et al reference do not cure the deficiencies of the Baker reference in view of the Penning et al and Oschlack et al. Applicant's arguments have been considered and are not persuasive for the reasons discussed supra.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

30 September 2005

PADMASHRI PONNALURI
PRIMARY EXAMINER